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Administrator

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October 19, 2006

Dear Administrator:

On behalf of the Flavor and Fragrance High Production Volume Consortia, I wish to thank the Environmental Protection Agency (EPA) for their comments on the test plan and robust summaries on "Bicyclic Terpene Hydrocarbons". The Terpene Consortium, as a member of FFHPVC, serves as an industry consortium to coordinate testing activities for chemical substances under the Chemical Right-to-Know Program. Since 1999, the companies that are current members of the Terpene Consortium have supported the collection and review of available test data, development of test plans and robust summaries, and conducted additional testing for "Bicyclic Terpene Hydrocarbons".

Based on our initial recommendations for testing and the peer-reviewed comments of the EPA, the Terpene Consortium of the Flavor and Fragrance High Production Volume Consortia (FFHPVC) is pleased to submit the following revised test plan and robust summaries for "Bicyclic Terpene Hydrocarbons". The revised test plan and robust summaries contain additional data on existing studies and the results of additional toxicity and environmental fate studies that are related to the questions and comments made by the EPA in its letter dated 03/11/2002. This letter contains responses to the specific comments made by the EPA. These responses taken together with the inclusion of new study data and other information constitute the key changes to the original test plan and robust summaries.

Based on these additional data, the Terpene Consortium concludes that the current test plan and robust summaries for this category is now complete. The experimental and model data for physiochemical properties, environmental fate, ecotoxicity, and human health endpoints are consistent and provide a comprehensive basis upon which to evaluate the hazard potential of monoterpene hydrocarbons. A summary of the key hazard data has been included in this letter and also in the revised robust summaries for the bicyclic monoterpene hydrocarbons category.

In an EPA letter dated 19 October 2001 concerning HPV-sponsored chemicals that are recognized as GRAS by the Food and Drug Administration, it was pointed out that:

" It may well be, on the basis of experience gained over years of use, that most of the substances have little compelling evidence suggesting that testing is needed in the context of the HPV Challenge Program. Nonetheless, while this line of reasoning could have been used to support the recommendation not to test the substances in this category, the information was only provided as background; few examples, and no actual data, were cited."

Without prior guidance from EPA, the Terpene Consortium felt responsible to report endpoint data for this substance. Most of these data have already been provided to the US Food and Drug Administration and the World Health Organization during their evaluation of these substances as food additives. Human health hazard data on bicyclic terpene hydrocarbons have been reviewed by the World Health Organization/Food and Agriculture Organization Joint Expert Committee for the Evaluation of Food Additives (WHO/FAO JECFA) for use as flavoring substances in food. As part of its responsibility, JECFA maintains on ongoing program of review of the safety of food additives (WHO Technical Series Nos. 38, 40, 42, 44, 46, 48, 50, 52, 54). In 2004, the group of bicyclic terpene hydrocarbons [WHO Food Additive Series: 52, 2004; see Revised Test Plan] were recognized as safe for use in food.

The group of substances in this chemical category is also recognized as "Generally Recognized as Safe" (GRAS) for its intended use in food by the United States Food and Drug Administration under the Code of Federal Regulations (CFR 172.515). Under supervision of the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences, specifications for the commercial use of monoterpene hydrocarbons in food are published in the Food Chemical Codex [FFC, 1996; see Revised Test Plan].

Based on the long history of use of bicyclic terpene hydrocarbons both as naturally occurring components of food and as substances intentionally added to food, the hazard assessments performed by the US FDA and WHO/FAO JECFA, and the current regulatory status for the addition of this substance to the food supply, there is no compelling evidence that this substance should be further tested for physiochemical properties and human health endpoints in the EPA Chemical "Right to Know" Program. We do, however, maintain that data on the environmental fate and ecotoxicity are relevant to the HPV Challenge program. In this context, we have sponsored ecotoxicity studies to provide a robust database on ecotoxicity endpoints. We consider that the test plan and robust summaries for this category are final and have no plans to provide additional data. The EPA

comprehensive comments provided the necessary guidance to complete the test plan for this category. The collaboration between the Terpene Consortium and the Environmental Protection Agency in the Chemical "Right to Know" Program has produced a hazard database that will be useful to the public for decades to come. Thank you for the opportunity to participate in such a program.

If you have any questions or comments concerning the contents of this letter, please feel free to contact me at any time (202-331-2325) or tadams@therobertsgroup.net.

Best regards,

Timothy B. Adams, Ph.D.

Technical Contact Person for FFHPVC

Summary of Key Hazard Data for Bicyclic Monoterpene Hydrocarbons

Endpoint	Substance/Surrogate[1]	Value/Range[2]	Reference
Physical Properties			
Vapor Pressure	*l-alpha*-pinene	0.53 kPa (25 °C)	Fichon, *et al*., 1999
	cis-pinane	0.73 kPa (25 °C)	Zhu *et a*l., 2003
	camphene	2.8 kPa (20 °C)	Hoechst AG, 1990
Partition Coefficient	*beta*-pinene	5.3 (OECD 117)	Dybdahl, 1993a
	delta-3-carene	5.5 (OECD 117)	Dybdahl, 1993a
	camphene	5.7 (OECD 117)	Dybdahl, 1993a
Environmental Fate			
Biodegradation	*alpha*-pinene	31d/37%/(OECD 302C)	Rudio, 1999a
		28d/38%/(OECD 301F)	Rudio, 1999b
	50.9% *alpha*-pinene + 36.8% *beta*-pinene	28d/52% (Sturm test)	Long, 2001b
	delta-3-carene	28d/<30% (OECD 301D)	Madsen, 1993b
	camphene	28d/<20%(OECD 301D)	Hoechst AG, 1988a
	alpha-pinene	8d/100% (forest soil samples)	Misra *et al.*, 1996
Ecotoxicity			
Fish	*alpha*-pinene	96-hr/LC50=0.28 mg/L	Broderius et al., 1990
	beta-pinene	96-hr/LC50=0.50 mg/L	Broderius et al., 1990
	camphene	96-hr/LC50=0.72 mg/L (OECD 203)	Hoechst AG, 1993
Aquatic Invertebrates	*alpha*-pinene	48-hr LC50 = 1.44 mg/L	Broderius et al., 1990
	beta-pinene	48-hr LC50 = 1.25 mg/L	Broderius et al., 1990
Aquatic Plants	*alpha*-pinene	48-hr EC50 = 0.973mg/L	Peterson, 1993
	beta-pinene	48-hr EC50 = 1.44 mg/L	Broderius et al., 1990

[1] Surrogate is a structurally related substance include a metabolic product or precursor of the named substance
[2] Experimental value or values for a substance or group of substances in the chemical category

Human Health			
Repeat Dose (route)	*alpha*-pinene (inhalation)	90-d LOAEL: 50 ppm (42 mg/kg bw/d (male); 400 ppm (340 mg/kg bw/d (female) (male rats exhibited α_{2u}-globulin nephropathy at all dose levels) 90-d NOAEL: 25 ppm (21 mg/kg bw/d (male); 200ppm (170 mg/kg bw/d (female)	NTP, 2006 EPA, 1990
	alpha-pinene (inhalation)	90-d LOAEL: 100 ppm (144 mg/kg bw/d (male and female mice); 90-d NOAEL: 50 ppm (72 mg/kg bw/d (male and female mice)	NTP, 2006
	camphene	28-d oral LOAEL =1000 mg/kg bw/d in male rats 28-d NOAEL=250 mg/kg/bw/d in male and female rats (male rats exhibited α_{2u}-globulin nephropathy at all dose levels)	Hoechst, 1991f
	verbenone (*alpha*-pinene -principal metabolite)	28-d 10 mg/kg bw/d. No effects (OECD 407 guideline study)	Jones, 2003
Reproductive	*alpha*-pinene (inhalation)	90-d 25, 50, 100, 200, 400 ppm males and female rats-no effects on reproductive organs or tissues	NTP, 2006
	alpha-pinene (inhalation)	90-d 25, 50, 100, 200, 400 ppm males and female rats-no effects on reproductive organs or tissues	NTP, 2006
	beta-myrcene (oral-gavage)	86-112 d NOEL= 300 mg/kg bw/d LOEL=500 mg/kg bw/d	Paumgartten et al., 1998
Developmental(route)	camphene (oral-gavage)	maternal NOEL (rat): 250 mg/kg bw/d developmental NOAEL=1000 mg/kg bw/d (oral-gavage)	Hoechst AG, 1992
in vitro Genotoxicity[3]	*alpha*-pinene, *beta*-	-(AMS); - (MLA); - (ABS); -	Rockwell and

[3] (-), no significant evidence; (+/-), equivocal evidence; (+), positive evidence of genotoxicity

	pinene and camphene	(SCE); - (UDS)	Raw, 1979; Florin *et al*., 1980; Heck *et al*., 1989; Jagannath, 1984; DeGraff, 1983; Connor *et al.,* 1985; Gomes-Carneiro, 2005; Sasaki *et al.*, 1989
in vivo Genotoxicity	*alpha*-pinene (inhalation)	(-) MN 90-day rats, 25-400 ppm	NTP, 2006
	alpha-pinene (inhalation)	(-) MN 90-day rats, 25-400 ppm	NPT, 2006
	camphene (oral-gavage)	(-) MN (4000 mg/kg bw/d)	Hoechst AG, 1991e

EPA Comments on Chemical RTK HPV Challenger Submission:

Bicyclic Terpene Hydrocarbons

SUMMARY OF EPA COMMENTS

The sponsor, the Flavor and Fragrance High Production Volume Consortia, submitted a test plan and robust summaries for the Bicyclic Terpene Hydrocarbons category to EPA on February 19, 2002. EPA posted the submission on the Chemical RTK HPV Challenge Web site on March 8, 2002.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. EPA considers the category to be reasonable.

2. Physicochemical Properties and Environmental Fate. The submitter needs to provide measured vapor pressure data for cis-pinane or dihydropinene and a technical discussion on a category read-across approach for the category members with no available measured biodegradation data. Also, EPA recommends that a Level III fugacity calculation be performed on these chemicals rather than the Level I calculations provided.

The vapour pressure for both *l-alpha*-pinene and *cis*-pinane have been determined. These dataare included in the robust summaries and test plan. Leve III fugacity calculations have been performed and included in the robust summaries.

3. Health Effects. The data submitted for the reproductive toxicity endpoint are inadequate. Unless the submitter can provide the necessary data to address this endpoint, additional testing is necessary for the purposes of the HPV Challenge Program. The submitter also needs to address deficiencies in the robust summaries.

Two ninety day inhalation studies have been performed for alpha-pinene in which a full complement of male and female sex organs and tissues were subjected to histopathological examination. Both studies reported no microscopic changes that could be associated with exposure to the test substance. Taking into account the lack of any effects to females in a recent teratology study, the absence of any maternal or developmental effects in a reproductive/developmental study of a pinene-based oil and for a structurally related monoterpene hydrocarbon, myrcene, it can be concluded that the members of this category show no significant reproductive or developmental toxicity.

4. Ecological Effects. Adequate data are available for toxicity to fish, aquatic invertebrates and algae for the purposes of the HPV Challenge Program. The submitter needs to provide missing data elements in the robust summaries.

Missing data has been added where available.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission

EPA COMMENTS ON THE BICYCLIC TERPENE HYDROCARBONS

CHALLENGE SUBMISSION

Category Definition

The chemical category includes six bicyclic terpene hydrocarbons and four mixtures composed primarily of *alpha*- and *beta*-pinene and smaller amounts of other terpene hydrocarbons. The category definition is adequate.

Category Justification

The submitter bases the category on structural similarities among category members and similar pathways of absorption, metabolism and excretion. There is no evidence that any member of the category will be atypical in terms of its chemical behaviour, environmental fate or toxicity. EPA considers this justification to be reasonable.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The data provided by the submitter for melting point, boiling point, partition coefficient and water solubility are adequate for the purposes of the HPV Challenge Program.

Vapor Pressure. EPA disagrees with the submitter's proposal to obtain vapor pressure test data for *alpha*-pinene to support estimated vapor pressure values for the other category members. EPA considers an SAR approach unnecessary because measured or extrapolated vapor pressure data exist for the majority of chemicals (including *alpha*-pinene and *beta*-pinene) in this category, with the exception of *cis*-pinane and dihydropinene. Therefore, the submitter needs to provide measured data (following OECD guidelines) for either cis-pinane or dihydropinene to complete the data set for this endpoint.

Experimental data have been generated for both for ***cis*-pinane and *l-alpha*-pinene (Fichon, *et al*., 1999; Zhu *et a*l., 2003). These data are in agreement with calculated values.**

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

Photodegradation and Stability in Water. The submitter's approach to these endpoints is adequate for the purposes of the HPV Challenge Program.

Biodegradation. The submitter provided adequate data demonstrating varying rates of biodegradation for alpha-pinene, camphene and turpentine gum. However, no experimental data were provided for other members of

the category and the BIOWIN estimates provided are not acceptable data for this endpoint. Based on the structural and physical similarities of bicyclic terpene hydrocarbon category members, these substances are also expected to biodegrade in the environment. The submitter needs to include in the test plan and robust summaries a technical discussion of a category read-across approach for those bicyclic terpene hydrocarbon category members with no available measured biodegradation data.

A discussion of biodegradation for the category has been included in the test plan.

Transport and Distribution (Fugacity). A Level III fugacity calculation should be performed on these chemicals rather than the Level I calculations provided. Although EPA had previously recommended the use of Level I, Level III modeling provides a more rigorous level of analysis.

Level III fugacity model calculations have been included in the revised robust summaries.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data are available for acute, repeated-dose, genetic, and developmental toxicity endpoints for the purposes of the HPV Challenge Program. The data submitted for the reproductive toxicity endpoint are inadequate. The submitter also needs to address deficiencies in the robust summaries.

Reproductive Toxicity. The three submitted studies by Morgareidge (1973a, 1973b, 1973c) are prenatal developmental toxicity studies rather than one-generation reproductive toxicity studies and therefore do not adequately address the reproductive toxicity endpoint. Although the reproductive toxicity endpoint can be addressed by documentation of the evaluation of reproductive organs in an existing 90-day repeated-dose toxicity study and an adequate developmental toxicity study, the data for all submitted 90-day repeated-dose toxicity studies are not reliable (submitter's assignment of Reliability Code 3). Therefore, EPA believes that the available information is inadequate to address this endpoint and that additional testing is necessary.

Ninety-day (90) studies in mice and rats have been performed by the National Toxicology Program. There were no adverse effects to any reproductive organs or tissues in both male and female rats and mice. When these data are combined with the fact that no adverse effects were observed to the reproductive organs in a 28-day developmental study with camphene [Hoechst AG, 1991f] at dose levels up to 250 mg/kg bw/day, it is concluded that bicyclic terpene hydrocarbons including *alpha*-pinene and *beta*-pinene exhibit no potential for reproductive toxicity. Also, a 91- day reproductive toxicity study has been performed for a structurally related monoterpene hydrocarbon, *beta*-myrcene. A NOAEL of 300 mg/kg bw per day has been reported. Additionally, a FDA study including evaluation of many parameters monitored in a standard reproductive toxicity study showed no evidence to conclude that these substances provided any significant reproductive hazard.

Developmental Toxicity. The submitted study by Hoechst AG (1992) was conducted according to OECD Guideline 414 and was given a reliability rating of 1. A supporting developmental toxicity study in rats with a terpene mixture was also submitted. Taken together, the data are adequate for the purposes of the HPV Challenge Program for this endpoint.

Ecological Effects (fish, invertebrates, algal toxicity)

Adequate data from three fish and two invertebrate toxicity tests are available to represent the category for these endpoints.

Algae. EPA considers three of the four submitted algal studies inadequate and the fourth to be of limited value. However, the ECOSAR evaluations provided by the submitter are adequate for the purposes of the HPV Challenge Program.

Specific Comments on the Robust Summaries

Environmental Fate.

Transport and Distribution (Fugacity). The submitter needs to include in the robust summaries all data input values used for modeling estimations. (See Guidance for Robust Summary preparation.)

Level III fugacity calculations include all input values in each of the appropriate robust summaries.

Health Effects.

Acute Toxicity. Information missing from the robust summaries includes: purity of the test chemical(s), age and body weight of the test animals, duration of observation period, and method for calculating toxicity values.

These data have been added.

Repeated-Dose Toxicity. In the 28-day (Hoechst AG 1991) study, the submitter needs to provide information on purity of test substance, frequency of data collection (for clinical signs, body weight, and food and water intake), specific hematology, clinical chemistry and urinalysis parameters examined, organs weighed and examined histopathologically, and statistical methods.

These data have been included when available in the published or unpublished report.

Genetic Toxicity. Missing information for the Ames test on *alpha*-pinene (Jagannath, 1984) and *beta*-pinene (DeGraff, 1983) includes: purity of test chemical, number of replicates/concentration (*beta*-pinene), criteria for positive and negative results, and number of metaphases per concentration examined. Missing details in the *in vivo* mouse micronucleus assay on camphene include: purity of test chemical, information on positive controls, number of cells examined, duration of exposure, and criteria for evaluating results.

These data have been included when available in the published or unpublished report.

Developmental Toxicity. The following details are missing from the OECD TG 414 study robust summary: purity of test chemical, fetal endpoints examined, and maternal LOAEL.

These data have been included when available in the published or unpublished report.

Ecological Effects.

Fish. The submitter needs to provide the following information for the reported EC50 values of 0.18 (CAS No.

80-56-8), 0.50 (CAS No. 127-91-3), and LC50 value of 0.72 mg/L (CAS No. 79-92-5): whether the EC50 and LC50 values are based on measured or nominal concentrations; control mortalities; age of fish at test initiation; pH, dissolved oxygen, and temperature readings throughout tests; statistical tests used and 95% confidence intervals for the LC50.

Requested data on physiochemical test parameters, mortalities, etc. were included in the robust summaries when available.

Invertebrates. The submitter needs to provide the following information for the reported EC50 values of 1.44 (CAS No. 80-56-8) 1.25 mg/L (CAS No. 127-91-3): method used to prepare the test concentrations; statistical tests use, and resulting 95% confidence intervals; age of the daphnids at test initiation; and ranges for the dissolved oxygen, pH, and temperature readings throughout tests.

Requested data on physiochemical test parameters, mortalities, etc. were included in the robust summaries when available.

Algae. The submitter needs to provide the following information for the reported EC50 value of 1.44 mg/L (CAS No. 127-91-3): water temperature, water hardness, dissolved oxygen, pH, statistical results, and chemical purity.

Requested data on physiochemical test parameters, mortalities, etc. were included in the robust summaries when available.